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Kunichika, Sango; Oka, Shinzaburo; Tanaka, Kazuhiko

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Sango KUNICHIKA, Shinzaburo OKA and Kazuhiko TANAKA*

(Kunichika Laboratory)

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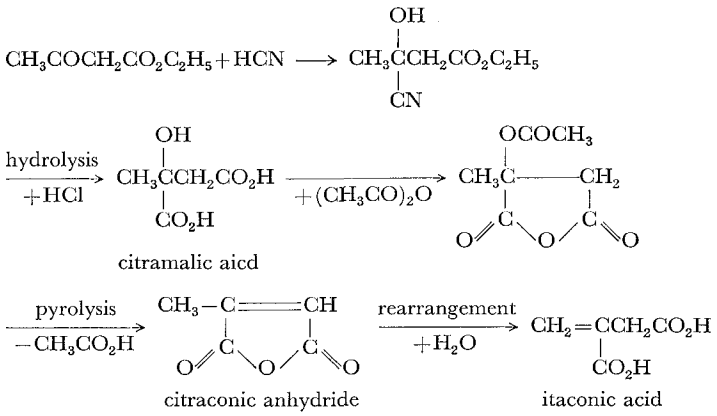
The synthesis of itaconic acid from ethyl acetoacetate via citraconic anhydride was attempted and the reaction conditions for every step were examined. Itaconic acid was obtained in the yield of about 85% from citraconic anhydride by heating it with the same amount of water at 170°C.

INTRODUCTION

It is known that itaconic acid is prepared by pyrolysis of citric acid[1] and commercially by fermentation of sugar cane. In the present work itaconic acid was synthesized by the following routes.



Consequently, satisfactory results were obtained in each process of the reactions.

EXPERIMENTAL

Acetoacetic ester cyanohydrin. A 500 ml four-necked flask, containing 130 g. of ethyl acetoacetate and 1.2 g. of potassium cyanide, was fitted with a stirrer, a thermometer, a condenser, and an inlet tube connected with a vessel containing 33.4 g. of hydrogen cyanide. The hydrogen cyanide was passed for three hours, in which time the temperature was kept at 5—10°C by immersing the flask in ice water. After the introduction of hydrogen cyanide was over, the reaction mixture was stirred for another fifteen minutes at that temperature. Then, 1 ml of concentrated sulfuric acid was added before distillation. The amount of fraction boiled at 133°C/23 mm was 145 g. (92.4%), $n_D^{25.7}$ 1.4296 (ref.[2] 120—124°C/13 mm, n_D^{25} 1.4298).

Citramalic acid. A mixture of 40 g. of acetoacetic ester cyanohydrin and

* 国近三吾，岡信三郎，田中和彦

41.2 g. of concentrated (35%) hydrochloric acid was refluxed until precipitation of ammonium chloride was over. Then, 200 ml of water was added and the mixture was refluxed for about four hours. After neutralizing with 7.5 g. of sodium bicarbonate, the water was removed under aspirator vacuum. When the evaporation was completed, the residue became a syrup and was extracted with 250 g. of etyhl acetate. The dried extract gave 26.8 g. (70.8%) of citramalic acid, m.p. 115°C (ref.[3] 119°C).

Anal. Calcd. for $C_5H_8O_5$: C, 40.54; H, 5.44.
Found: C, 40.39:; H, 5.54.

α-Methyl-α-acetoxy succinic anhydride. A mixture of 26 g. of citramalic acid and 72 g. of acetic anhydride was refluxed with 0.5 g. of concentrated sulfuric acid for six hours. Distillation of the reaction mixture gave 27.1 g. (89.8%) of α-methyl-α-acetoxy succinic anhydride, b.p. 147°C/12 mm. $n_D^{24.3}$ 1.4475.

Anal Calcd. for $C_7H_8O_5$: C, 48.84; H, 4.68.
Found: C, 48.60; H, 4.77.

Citraconic anhydride. The pyrolysis of 10 g. of α-methyl-α-acetoxy succinic anhydride under a nitrogen atmosphere (13 mm Hg) gave a mixture of citraconic anhydride and acetic acid, from which 4.8 g. (73.7%) of citraconic anhydride was obtained. b.p. 94°C/14.5 mm, $n_D^{19.3}$ 1.4720 (ref.[4,5] b.p. 105–110°C/22 mm, $n_D^{21.3}$ 1.4710). Its infrared spectrum showed the characteristic absorption bands at 1843 (C=O), 1765 (C=O) and 1647 cm^{-1} (C=C), and it was identical with that of an authentic sample.

Itaconic acid. Citraconic anhydride and water were weighed into a glass tube, which was sealed, and was heated in a shaking type autoclave charged with water. The sealed tube was then cooled for one day in a refrigerator. The itaconic acid crystallized out was filtered by suction, dried in a vacuum desiccator over phosphorous pentoxide, and weighed, m.p. 165–166°C (ref.[7] 165–166°C). Its infrared spectrum was identical with that of an authentic sample.

Anal. Calcd. for $C_5H_4O_3$: C, 46.26; H, 4.85.
Found: C, 46.16; H, 4.65.

RESULTS

Preparation of acetoacetic ester cyanohydrin.

Mowry et al.[2] reported that acetoacetic ester cyanohydrin was obtained in a yield of 85% from ethyl acetoacetate. In the present work, the yield of the cyanohydrin could be raised by proper secletion of reaction conditions. The results are shown in Table 1.

The lower the temperature, the higher was the yield of the cyanohydrin. This result may be interpreted as due to that the addition of hydrogen cyanide is reversible and exthothermic. The yield was hardly affected by the amount of potassium cyanide which was added as a catalyst.

Table 1. Preparation of acetoacetic ester cyanohydrin
Ethyl acetoacetate, 130 g.; hydrogen cyanide, 33.4 g.

Reaction temp. °C	Reaction time min.	Amount of KCN g.	Yield g. (%)
20–25	193	1.2	130.3(82.8)
"	210	"	130.8(83.2)
5–10	192	"	140.9(89.6)
"	207	"	145.3(92.4)
"	226	"	143.5(91.3)
"	212	2.4	141.9(90.3)

Preparation of itaconic acid.

Although the thermal rearrangement of citraconic acid or citraconic anhydride to itaconic acid in an aqueous solution has been reported, little information was available on the factors that governed the formation of itaconic acid. In the present study this rearrangement was examined to find suitable conditions for the reaction.

Effect of the amount of water A mixture of various ratio of citraconic anhydride and water was heated according to the procedure described in the Experimental part. The results are given in Table 2.

Table 2. Effect of the amount of water
Reaction temperature, 150°C; reaction time, 3 hrs.
Citraconic anhydride, 10 g.

Water g.	Yield of itaconic acid %
2[a]	14.7
5[b]	22.4
10	45.0
30[c]	40.5
50[c]	33.6
80[c]	19.0

a) After reaction was over, 8 g. of water was added to the reaction mixture.
b) 5 g. of water was also added.
c) After reaction, the mixture was concentrated to the total weight of 20 g.

The yield of itaconic acid had the maximum when the same amount of water and citraconic anhydride was used.

Effect of the reaction temeprature The rearrangement reaction was studied in the range 140–200°C. The results are recorded in Table 3 and the variation of yield is given in Fig. 1.

Table 3. Effect of the reaction temperature
Citraconic anhydride, 10 g.; water, 10 g.

Run	Reaction temp. °C	Reaction time hrs.	Yield of itaconic acid %
1	140	6.0	37.9
2	"	9.0	46.5
3	150	3.0	45.7
4	"	6.0	50.8
5	160	2.0	48.3
6	"	3.0	55.2
7	"	4.0	54.3
8	"	6.0	50.0
9	170	1.0	51.7
10	"	2.0	56.8
11	"	4.0	52.6
12	180	1.0	54.3
13	190	"	44.8[a]
14	200	"	45.7[a]
15[b]	180	"	56.0
16[c]	"	2.0	0

a) Itaconic acid obtained was contaminated with mesaconic acid.
b) Instead of citraconic anhydride, 11.6 g. of itaconic acid was used.
c) A mixture of 13.2 g. of citramalic acid and 6.8 g. of water was used.

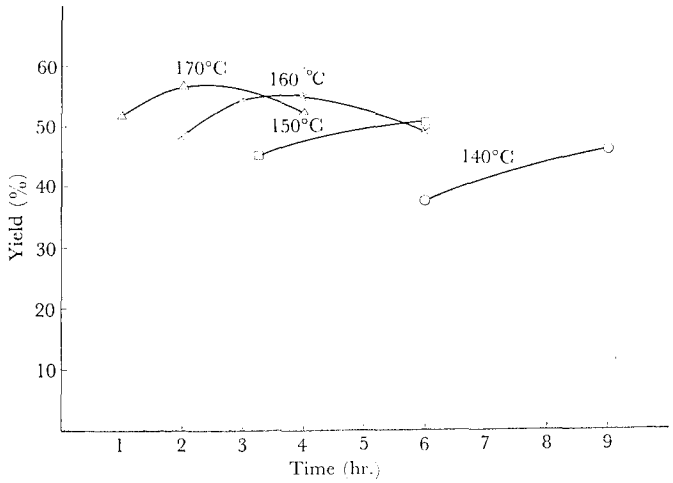


Fig. 1. Effect of the reaction temperature.

With elevation of the reaction temperature, the yield of itaconic acid increased in the range 140–170°C. At above 180°C, the yield decreased and a considerable amount of mesaconic acid, trans-isomer of citraconic acid, was observed. Mesaconic acid was also formed at 150°C when small amount of mineral acid such as hydrochloric acid or hydrobromic acid was added. It is of interest that citramalic acid was not converted to itaconic acid as shown in run 16. It shows that citramalic acid is not the

intermediate in the thermal rearrangement of citraconic anhydride or citraconic acid to itaconic acid. From both citraconic anhydride and itaconic acid, the same amount of itaconic acid was obtained as shown in runs 12 and 15. These results show that an equilibrium exists between citraconic acid and itaconic acid. Thus a temperature of 170°C and the reaction time of two hours were found to be optimum for the synthesis. Instead of recovering citraconic anhydride from the mother liquor it is more favorable to repeat the following procedure: that is, after separation of itaconic acid by the method described in the Experimental parts, the equimole of citraconic anhydride to itaconic acid separated was added to the mother liquor and the mixture was heated again. After repeating the above prodcedure five times, citraconic anhydride was recovered by distilling the mother liquor since it was contaminated with various by-products. As shown in Table 4, itaconic acid was obtained in a yield of 85% based on the amount of citraconic anhydride consumed.

Table 4. Preparation of itaconic acid.

	1 hr. at 170°C		2 hrs. at 160°C	
	Citraconic anhydride g.	Itaconic acid g.	Citraconic anhydride g.	Itaconic acid g.
1st	10.0	6.1	10.0	5.3
2nd	5.1	5.5	4.6	5.9
3rd	4.9	5.0	5.2	4.9
4th	4.2	4.5	4.3	5.2
5th	3.8	4.1	4.6	4.9
Total	28.0	25.2	28.7	26.2
Citraconic anhydride recovered	2.3	—	2.1	—
Total yield (%)		84.5		84.6

The quantitative analysis of the mixture containing itaconic acid, citraconic acid, mesaconic acid, and citramalic acid by gas chromatography or infrared spectroscopy was very difficult. However, the analysis of the mixture of esters of the above four acids was successfully made by using a 90 m butanediol succinate polyester-coated capillary colum at 148°C. More details on the rearrangement would be clarified by using this analytical method.

REFERENCES

(1) R.L. Shriner et al., "Org. Syntheses", Coll. Vol. II, 368 (1956).
(2) D.T. Mowry et al., *J. Am. Chem. Soc.*, **67,** 928 (1945).
(3) Michael, *J. für prakt. Chem.* [2] **46,** 287 (1892).
(4) C. Knops, **Ann. 248,** 199 (1888).
(5) R.L. Shriner et al., "*Org. Syntheses*", Coll. Vol. II, 140 (1956).
(6) R.P. Linstead et al., *J. Chem. Soc.*, **1931,** 734.
(7) R. Fittig et al., **Ann. 188,** 72 (1877).